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(54) Title: METHOD OF EVALUATING THE EFFICACY OF DRUG ON BRAIN NERVE CELLS

(57) Abstract

The present invention relates to a method to measure *in vivo* the effect of a drug on the function of the nerve cells of the brain of a patient suffering from a neurological disease, which comprises the steps of: a) measuring NAA signal intensity using MRS of the brain of the patient; b) subjecting the patient to a treatment with the drug to be tested and measuring NAA signal intensity using MRS of the brain of the patient; and c) comparing the spectra of steps a) and b) to determine whether the drug has an effect on the function of the nerve cells of the brain; whereby the increase in the NAA signal of step b) is indicative of a drug with a positive effect.

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METHOD OF EVALUATING THE EFFICACY OF DRUG
ON BRAIN NERVE CELLS

BACKGROUND OF THE INVENTION

5 (a) Field of the Invention

The invention relates to a method of evaluating
the efficacy of drugs on brain nerve cells based on the
use of proton magnetic resonance spectroscopy.

(b) Description of Prior Art

10 Amyotrophic lateral sclerosis (ALS) is a pro-
gressive, usually sporadic form of motor neuron disease
(MND) affecting both the upper motor neurons (UMNs) and
the lower motor neurons (LMNs). The motor neurons are
the postulated primary targets of the disease process.
15 The relationship of MNDs involving solely the UMNs
(primary lateral sclerosis (PLS)) or LMNs (progressive
spinal muscular atrophy (PSMA)) with ALS remains to be
established. Pure LMN syndromes may be present in
hexosaminidase deficiency and immune-associated syn-
20 dromes which, in some cases, may be amenable to spe-
cific therapies.

Magnetic resonance spectroscopy (MRS) is similar
to conventional magnetic resonance imaging (MRI), and
is performed using basically the same equipment with
25 relatively minor hardware and software modifications.
However, whereas MRI provides *anatomical* information
based on signals from water, MRS provides *chemical*
information from metabolites that are present in tis-
sues at much lower concentration than water.

30 Proton magnetic resonance spectroscopic imaging
(^{1}H-MRS) provides the ability to noninvasively evaluate
regional chemical pathology of human brain *in vivo*.
Proton MR spectra of human brain reveal two signals of
interest for this application: a signal from N-acetyl
35 groups (mainly N-acetylaspartate) (NAA) and a signal
from creatine (Cr). NAA is found exclusively in neu-

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rons and neuronal processes in the normal mature brain
(Moffett JR, Namboodiri MAA, Cangro CB, Neale JH, 1991,
NeuroReport, 2:131-134; Simmons ML, Frondoza CG, Coyle
JT, 1991, Neuroscience, 45:37-45) and, thus, can be
used as a marker of neuronal integrity. Cr is present
in all cells of the brain and can be used as an inter-
nal standard. The expression of NAA signal intensity
relative to Cr (NAA/Cr) allows for easy comparison of
NAA signal intensity (and, by implication, neuronal
integrity) between different subjects.

^{1}H-MRS can be used to assess and monitor the
evolution of neuronal or axonal damage in various con-
ditions, including MS, stroke, human immunodeficiency
virus-associated cognitive impairment and Alzheimer's
disease.

A major problem in assessing drug efficacy in
neurodegenerative disease is the lack of efficient
clinical outcome measures. As a result of this, large
multicenter trials are generally necessary. Such tri-
als cost many millions of dollars, and may produce
negative results, as did recent trial of ciliary neuro-
notropic factor and brain-derived neuronotropic factor.
An efficient surrogate marker of efficacy would, there-
fore, be extremely valuable.

MRS has been used for a number of years now to
assess neuronal and axonal loss based on the signal
intensity of N-acetyl groups, which comes primarily
from NAA in brain. The Applicants have used the signal
to quantify the severity of disease and follow its pro-
gression based on decreases in NAA over time. Recently,
we have reported the fact that decreases in NAA can
spontaneously recover with time after certain brain
injuries (multiple sclerosis relapses and some kinds of
stroke). (De Stefano N, Matthews PM, Arnold DL, 1995,
Magn. Reson. Med., 34:721-727).

However, to date there exist no means to assess *in vivo* whether a drug has any positive effect on the brain function of a patient, such as restoring its NAA signal.

SUMMARY OF THE INVENTION

In accordance with the present invention, the Applicants have now discovered that abnormally low NAA levels can made to increase with effective drug therapy in patients with amyotrophic lateral sclerosis (ALS). This indicates that NAA can be used as a marker of improved neuronal function as well as a marker of neuronal loss. The use of MRS to measure increases in NAA as a marker of drug efficacy is novel and provides unexpected and unprecedented results.

In accordance with the present invention there is provided a method to measure *in vivo* the effect of a drug on the function of the brain of a patient suffering from a neurologic disease, which comprises the steps of:

a) obtaining ^{1}H-MR spectra of the brain of the patient and measuring the signals from NAA;

b) subjecting the patient to a treatment with the drug to be tested and measuring the signals from NAA in the brain of the patient; and

c) comparing the spectra of steps a) and b) to determine whether the drug has an effect on the function of nerves cells in the brain; whereby the increase in the NAA signal of step b) is indicative of a drug with a positive effect.

The term "neurologic diseases" when used herein is intended to mean, any neurologic diseases including strokes, multiple sclerosis, amyotrophic lateral sclerosis, epilepsy and neurodegenerative diseases such as Alzheimer's disease among others.

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This invention can also be used to monitor drug improvement produced by treatment of other neurodegenerative diseases for which NAA decline has been observed with disease progression (such as Alzheimer's
5   disease). Moreover, spontaneous improvement with time in NAA observed in certain types of cerebrovascular insults, and in acute exacerbations of multiple sclerosis (DL. Arnold et al., 1992, *Proc. Soc. Magn. Reson. Med.*, **1**:643; N. De Stefano et al., 1995, *Neurology*,
10 **45**:1193-1198; N. De Stefano et al., 1995, *Magn. Reson. Med.*, **34**:721-727) also indicate that drug therapies for these disorders may be tested in MRSI to assay for more complete or more rapid NAA recovery with novel drug therapies. This invention will help identify agents
15 useful to human neurological therapeutics before the initiation of full scale clinical trials, and will help identify dosing regiments that may be most effective in such clinical trials.

20 **BRIEF DESCRIPTION OF THE DRAWINGS**

Fig. 1A illustrates an MRI with superimposed phase-encoding grid for MRSI in a patient with ALS with the voxels in the precentral gyrus of both hemispheres labeled with solid circles;
25 Fig. 1B illustrates the averaged MRI spectra from voxels in the precentral gyrus of a patient with ALS before and after and after 3 weeks of treatment with Riluzole™; and

Fig. 2 illustrates a bar graph showing the mean
30 change in NAA/Cr in 11 patients treated with Riluzole™ (ALS-R) compared to 12 patients who received no treatment (ALS-C).

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided the use of proton MRS to monitor therapeutic efficacy on neuronal function based on increases in
5 the signal from the neuronal marker, NAA. In accordance with the present invention, we have demonstrated the principle in the case of Riluzole™ treatment for ALS. ALS is a neurodegenerative disease in which glutamate excitotoxicity is believed to play a pathogenetic
10 role. Riluzole™, a glutamate release inhibitor antagonist, has been demonstrated in phase III clinical trials to prolong the life of patients with ALS (Bensimon G, Lacomblez L, Meininger V, 1994, *N. Engl. J. Med.*, **330**:585-591; Lacomblez L, Bensimon G, Leigh PN, Guillet
15 P, Meininger V, 1996, *Lancet*, **347**:1425-1431). We used proton MRS to monitor the signal intensity of NAA in the motor cortex of patients with ALS and succeeded in detecting an acute (within 3 weeks) increase in the signal from NAA after Riluzole™ treatment (Figs. 1A and
20 1B).

Figs. 1A and 1B illustrate an example based on a patient with ALS treated with Riluzole™ showing an acute (3 weeks) increase in the signal from NAA in his motor cortex with respect to Cr. Inset shows a conven-
25 tional MRI with the phase-encoding grid for spectroscopic imaging superimposed and the motor cortex outlined with a dashed line. Spectrum before treatment shows lower NAA than normal. Spectrum after treatment shows increased NAA suggesting improved neuronal func-
30 tion.

The demonstration of this phenomenon is valuable as it may provide a surrogate marker of response, as well as providing information on dosing and individual patient responsiveness to treatment.

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In accordance with the method of the present invention, treatments may be tested to determine their effect on the function of brain. Such treatment includes any therapeutic agent, the action of which is
5 directed at neurons, such as Riluzole™, Gabapentin, zidovudine and sodium dichloroacetate.

This invention can also be used to monitor drug improvement produced by treatment of other neurodegenerative diseases for which NAA decline has been
10 observed (such as Alzheimer's disease). Moreover, spontaneous improvement with time in NAA observed in certain types of cerebrovascular insults, and in acute exacerbations of multiple sclerosis (DL. Arnold et al., 1992, *Proc. Soc. Magn. Reson. Med.*, **1**:643; N. De
15 Stefano et al., 1995, *Neurology*, **45**:1193-1198; N. De Stefano et al., 1995, *Magn. Reson. Med.*, **34**:721-727) also indicate that drug therapies for these disorders may be tested by MRS to assay for more complete or more rapid NAA recovery with novel drug therapies. This
20 invention will help identify agents useful to human neurological therapeutics before the initiation of full scale clinical trials, and will help identify dosing regiments that may be most effective in such clinical trials.
25 The present invention will be more readily understood by referring to the following examples which are given to illustrate the invention rather than to limit its scope.

EXAMPLE I

30 **MRS methods of the present invention used for
the detection of increased NAA in response to
Riluzole™ treatment**

Nineteen patients with a diagnosis of definite
35 or probable ALS, as per the El Escorial Criteria,[12] were recruited. Each patient underwent paired MRSI examina-

tions.   Eleven had their first scan just before com-
mencing treatment and a second approximately three
weeks after starting Riluzole™ (50 mg bid); this group
was designated ALS-R.   Nine patients opting for no
5   treatment had paired scans separated by approximately 3
weeks.   Of the 11 treated patients 3 had had an addi-
tional scan approximately 3 weeks before starting
treatment.   Thus, closely paired MRSIs were obtained
off medication in 12 subjects who formed a disease con-
10   trol group ALS-C.

Magnetic Resonance Spectroscopic Imaging

Brain proton spectroscopy was performed using a
Philips Gyroscan ACS3 operating at 1.5 Tesla (Philips
Medical System, Best, The Netherlands).   After axial
15   and sagittal scout images and sagittal T1-weighted
images were obtained, axial T1-weighted images were
acquired with an angulation determined from sagittal
T1-weighted images such that the transverse plane was
perpendicular to the rostral-caudal axis of the precen-
20   tral gyrus.   These transverse scans were used to select
a volume of interest (VOI) centered on the central sul-
cus, high in the cranium comprised of predominantly
cortical brain (Fig. 1A).   Cranio-caudal (CC) thickness
was 20 mm.   Anteroposterior (AP) and left-right (LR)
25   dimensions were adjusted for each patient depending on
the skull size and shape to maximize size without
including skull.   MRSI was performed using a 90° - 180°
- 180° (PRESS) sequence (TR=1750, TE=272, 250x250mm FOV,
32x32 phase-encoding steps) with prior suppression of
30   water by selective excitation.   One patient had all his
scans performed with TR=1500.   The ROI was repositioned
in the identical location in follow up scans of each
patient.

^{1}H-MRS data post-processing

Post-processing of data, included a mild Gaussian filter and an inverse two-dimensional Fourier transform of both the water-suppressed and -unsuppressed ^{1}H-MRS. This was accomplished with XUNSPEC1 software (Philips Medical Systems Best, The Netherlands) running on a Sun SPARC™ station.

The residual water signal was removed using the HSVD (Hankel Singular-Value Decomposition) algorithm which models the time-domain ^{1}H-MRS data in each voxel with exponentially damped sinusoids. Peaks used to model the water signal were then subtracted from the original data. This algorithm is fully automatic and requires no prior knowledge or operator intervention.

^{1}H-MRS data reduction

Automated calculation of metabolite peak areas was performed on operator-selected voxels within the motor cortex. Peaks were digitally integrated to yield areas. These values were normalized by dividing them by that of Cr.

Statistical Methods

The NAA/Cr of the primary motor cortex was determined by averaging the NAA/Cr intensities of voxels located in the precentral gyrus of both hemispheres (Figs. 1A and 1B). The difference in motor cortex NAA/Cr between two scans (ΔNAA/Cr) obtained approximately 3 weeks apart was determined for each ALS patient in the treated (ALS-R) and control (ALS-C) groups. ΔNAA/Cr was compared between the treated and control groups using a two-sample two-sided Student's t-test. In addition, a two-sided paired Student's t-test was used to evaluate the significance of ΔNAA/Cr within each group.

Results

Nineteen patients with ALS (7 females, 12 males, average age 64 ± 11 years, baseline NAA/Cr 2.19 ± 0.21) were studied. Demographic characteristics, motor cor-
5   tex NAA/Cr observed in paired scans, and the change in NAA/Cr between paired scans are presented in Table 1. There was no statistically significant difference in sex, age, disease duration, baseline NAA/Cr, or fre-quency of upper motor neuron or bulbar involvement
10   between the ALS-R and ALS-C groups.

Approximately 24 ± 8 days after initiating Rilu-zole™ therapy in 11 patients (ALS-R) the average NAA/Cr for the group increased from 2.14 ± 0.26 to 2.27 ± 0.24 (mean ± SD, p=0.044). In 12 patients not receiving
15   medication (ALS-C) the average NAA/Cr for the group decreased from 2.17 ± 0.20 to 2.08 ± 0.20 (mean ± SD, p=0.099) over a period of 21 ± 6 days. Thus, the change in NAA/Cr for the treated group with respect to the untreated group was an increase of 0.22 ± .095
20   (mean ± SE, p=0.008) (Fig. 2). Note the rise in NAA/Cr after approximately 3 weeks of treatment with Riluzole™ versus the decrease in the untreated group. Standard error bars are shown.

Absolute motor cortex Cr signal intensities did
25   not change between paired exams in either the treated (p=0.89) or untreated groups (p=0.97).

In patients treated with Riluzole™, there was no significant correlation between ΔNAA/Cr and age, pre-treatment NAA/Cr, and duration of treatment or dis-
30   ease. There was no difference in ΔNAA/Cr with Rilu-zole™ treatment between males or females, patients with

definite or probable UMN signs, and patients with or without bulbar features.

Only one patient described symptomatic and functional changes during the few weeks of therapy between two scans: patient #11 described improved strength and reduced disability (less difficulty raising arms and climbing stairs) after 35 days of Riluzole™ therapy. Deltoid and iliopsoas MRC grades improved bilaterally from 4 to 4+.

Several patients agreed to longer term follow up studies. In patient #2, NAA/Cr increased from 2.53 to 2.64 after 35 days of Riluzole™ therapy; three months later it increased further to 2.74, at which time he reported increased strength and fewer cramps. In patient #3, NAA/Cr increased from 2.00 to 2.44 after 18 days of Riluzole™ therapy; three months later it had dropped to 1.46 associated with significant clinical deterioration including increased dysarthria and weakness. In patient #5, NAA/Cr increased from 2.24 to 2.31 after 21 days of therapy and further to 2.42 one year later; weakness, with predominantly LMN features, slowly progressed. Patient #17 was never treated: NAA/Cr decreased from 2.51 to 2.42 after 21 days and further to 2.11 4 months later; his symptoms progressed slowly.

Discussion

Using proton MRSI to measure the neuronal marker NAA, we have demonstrated a rise in the relative intensity of NAA in the primary motor cortex of patients with ALS within 3 weeks of starting Riluzole™ therapy. Longer-term follow-up scans revealed some correlation between the changes in NAA/Cr and the clinical status of several patients.

Low NAA/Cr *in vivo* has been observed in numerous neurological disorders associated with neuronal loss or damage, and appears to result from either: (i) a decrease in the intracellular volume of neurons per unit volume of brain (due to either neuronal loss or atrophy), or (ii) a decrease in the concentration of NAA within neurons due to metabolic dysfunction. [13-19]

Recovery of NAA has been observed in a variety of situations associated with recovery of neuronal integrity; for example, in patients recovering from acute demyelinating lesions or strokes, after successful surgery for temporal lobe epilepsy or carotid occlusive disease, and after instituting anti-retroviral therapy in AIDS.

As discussed by De Stefano, reversible changes in NAA/Cr most likely result from either an increase in the volume of NAA-containing neurons (including dendrites and axons) per unit volume of brain or an increase in the concentration of NAA within neurons. Since CNS neurons have a limited capacity to regenerate, increases in relative neuronal volume would have to result from increases in the volume of existing neurons. Dendritic atrophy has been reported in ALS. Reversal of neuronal atrophy, for example, due to dendritic sprouting, may be contributing to the observed increases in NAA/Cr in response to Riluzole™ therapy. Increases in the concentration of NAA within neurons may also be contributing to the observed increases in NAA after Riluzole™ therapy. Mitochondria can be injured by glutamate-mediated excitotoxicity. NAA is synthesized in the mitochondria of neurons, and inhibition of the mitochondrial respiratory chain is known to result in diminished NAA production, Therefore, reduced

glutamate-mediated excitotoxic mitochondrial damage could lead to increases in the concentration of NAA within neurons after instituting Riluzole™ therapy.

It is unlikely that the observed changes in NAA/Cr represent a methodological artifact. There is no theoretical reason to expect a change in the relaxation properties of NAA with respect to Cr in the patients who were treated *vs.* those who were untreated. Possible effects of differences in the content of white and grey matter would similarly not be expected to systematically affect the treated group. Finally, *in vitro* studies using high performance liquid chromatography to measure NAA in cultured neuronal cells also show reversible decreases in NAA after metabolic stress.

Conclusions

Assessment of corticomotoneuron integrity and function is difficult in ALS. Commonly used clinical outcome measures reflect both upper and lower motor neuron dysfunction. This study demonstrates that MRSI can be used to monitor specifically an improvement in UMN integrity, which is otherwise difficult to detect and quantify. Changes in NAA could thus provide an important and useful surrogate marker for therapeutic response. Although the augmentation of NAA/Cr in motor cortex does not necessarily imply that neuronal survival will be extended with corresponding clinical benefit, these clinical benefits have already been demonstrated for Riluzole™ therapy of ALS. Thus, we believe that the potential for NAA/Cr to become a valid surrogate for therapeutic response in ALS is promising.

Table 1

Patient Characteristics and Data

Patient Treated (ALS-R) n = 11	Age	Sex	Disease Duration (months)	El Escorial designation	Bulbar features[¶]	UMN features[¶]	NAA/Cr MRSI #1[£]	NAA/Cr MRSI #2[£]	ΔNAA/Cr
1	74	m	24	definite	Yes	Yes	2.519	2.508	-0.011
2	35	m	12	definite	Yes	Yes	2.532	2.643	0.111
3	56	m	2	definite	Yes	Yes	2.004	2.442	0.438
4	73	f	24	probable	No	Probable	2.121	2.416	0.295
5	67	f	36	probable	No	probable	2.305	2.423	0.118
6	78	f	24	definite	No	probable	2.057	2.291	0.234
7	55	f	24	probable	No	probable	1.911	1.890	-0.021
8	68	m	32	probable	No	probable	2.334	2.083	-0.251
9	61	f	12	probable, familial	Yes	probable	2.025	2.247	0.222
10	75	m	36	probable	Yes	Yes	1.679	1.969	0.290
11	57	f	180	probable, familial	No	Yes	2.019	2.053	0.034
Mean	64		37				2.14	2.27	0.13
SD	13		49				0.26	0.24	0.19

Patient Control (ALS-C) n = 12	Age	Sex	Disease Duration (months)	El Escorial designation	Bulbar features[¶]	UMN features[¶]	NAA/Cr MRSI #1[£]	NAA/Cr MRSI #2[£]	ΔNAA/Cr
5	67	f	36	probable	No	probable	2.235	2.305	0.070
6	78	f	24	definite	No	probable	2.009	2.057	0.048
7	55	f	24	probable	No	probable	2.002	1.911	-0.091
10	75	m	36	probable	Yes	Yes	2.284	1.907	-0.377
12	77	m	12	definite	No	Yes	2.320	2.141	-0.179
13	71	f	36	probable	No	probable	1.901	2.003	0.102
14	65	m	120	definite	Yes	Yes	2.033	1.830	-0.203
15	79	m	36	definite	Yes	Yes	2.148	1.826	-0.322
16	62	m	10	definite	Yes	No	1.915	2.110	0.195
17	50	m	72	definite	Yes	Yes	2.515	2.422	-0.093
18	63	m	144	probable	Yes	Yes	2.157	2.039	-0.118
19	51	m	6	probable	Yes	Yes	2.459	2.358	-0.101
Mean	66		46				2.17	2.08	-0.09
SD	10		44				020	0.20	0.17

UMN = Upper Motor Neuron
[¶] Criteria for UMN and bulbar involvement per El Escorial Criteria
[£] NAA/Cr of motor cortex
ΔNAA/Cr = Change in NAA/Cr between MRSI scan #1 and # 2

While the invention has been described in con-
nection with specific embodiments thereof, it will be
understood that it is capable of further modifications
and this application is intended to cover any varia-
5   tions, uses, or adaptations of the invention following,
in   general,   the   principles   of   the   invention   and
including such departures from the present disclosure
as come within known or customary practice within the
art to which the invention pertains and as may be
10   applied to the essential features hereinbefore set
forth,   and   as   follows   in   the   scope   of   the   appended
claims.

WHAT IS CLAIMED IS:

1.   A method to measure *in vivo* the effect of a drug on the function of the nerve cells of the brain of a patient suffering from a neurological disease, which comprises the steps of:

   a)   measuring NAA signal intensity using MRS of the brain of the patient;

   b)   subjecting the patient to a treatment with the drug to be tested and measuring NAA signal intensity using MRS of the brain of the patient; and

   c)   comparing the spectra of steps a) and b) to determine whether the drug has an effect on the function of the nerve cells of the brain; whereby the increase in the NAA signal of step b) is indicative of a drug with a positive effect.

2.   The method of claim 1, wherein the drug to be evaluated is selected from the group consisting of Riluzole™, Gabapentin, zidovudine and sodium dichloroacetate.

3.   The method of claim 1, wherein the neurologic disease is selected from the group consisting of strokes, multiple sclerosis, amyotrophic lateral sclerosis, epilepsy and neurodegenerative diseases.

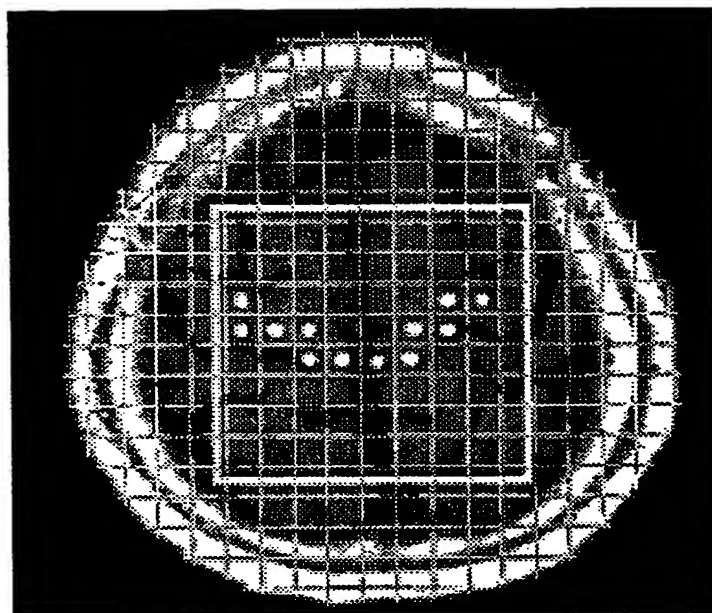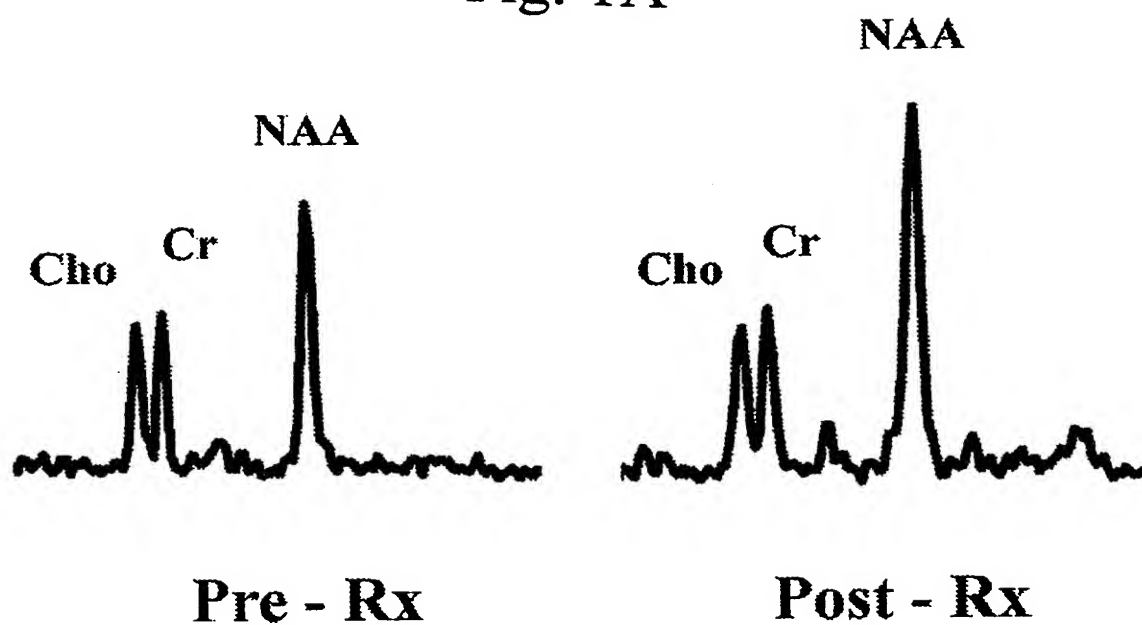4.   The method of claim 3, wherein the neurodegenerative disease is Alzheimer's disease.
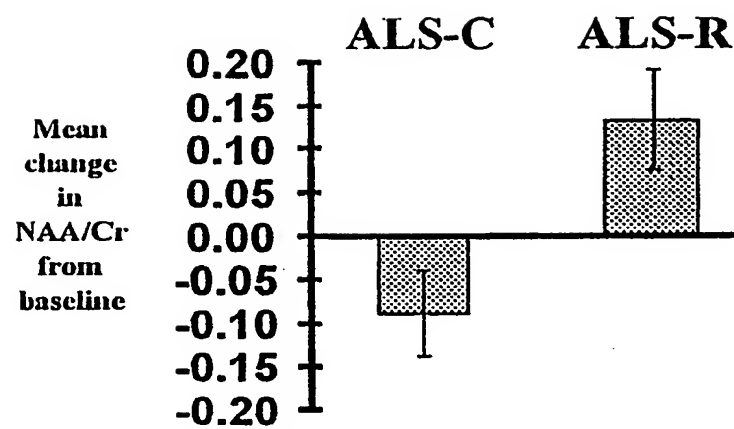
Fig. 1A

Pre - Rx

Post - Rx

Fig. 1B

Fig. 2

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6   G01R33/483

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6   G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N. DE STEFANO ET AL.: "Reversible Decreases in N-Acetylaspartate ..." MAGNETIC RESONANCE IN MEDICINE, vol. 34, 1995, pages 721-727, XP002068858 cited in the application see the whole document	1-4
X	D.L. ARNOLD: "Reversible Reduction of N-acetylaspartate ..." SOCIETY OF MAGNETIC RESONANCE IN MEDICINE, 11TH MEETING, 1992, page 643 XP002068859 cited in the application see the whole document	1-4

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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 1998	06/07/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Volmer, W

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	N. DE STEFANO ET AL.: "Correlation between brain lesion load on MRI ..." SOCIETY OF MAGNETIC RESONANCE, 3RD MEETING, 1995, page 57 XP002068907 see the whole document	1-4
P,X	US 5 617 861 A (B. ROSS ET AL.) 8 April 1997 see the whole document	1-4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Int ;ional Application No

PCT/CA 98/00230

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5617861 A	08-04-1997	NONE	